Remarks/Arguments:

The Office Action rejects claims 1-19 and 21-39 under U.S.C. § 102(b) as being anticipated by Desai et al. US 5916596. The Office Action also makes multiple rejections under U.S.C. § 103(a). Claims 1-19 and 21-39 [sic. 38] are rejected as being unpatentable over Parikh et al. US 5922355 in view of Chagnon et al US 5389377, and claims 1-7, 11, 21-39 [sic. 38] are rejected as being unpatenable over Desai et al. US 5916596.

Applicants respectfully point out that the previous Amendment erroneously numbered the last claim in this application. The present paper changes claim 39 to claim 38, and hereinafter applicants refer to claim 38 rather than claim 39 (as presented in the Office Action).

Concerning the § 102(b) rejection, the Office suggests that Desai's method of sonicating an emulsion teaches the invention claimed by the applicants. However unlike applicants, Desai dos not teach sonication of an emulsion to evaporate a water immiscible organic solvent to cause a pharmaceutically active agent, dissolved in the organic solvent, to precipitate into the aqueous phase and form particles. Instead Desai uses sonication to create: 1) nanodroplets that contain dissolved pharmaceutically active compounds, and 2) a crosslinked biocompatible (e.g. protein) coat that encapsulates the pharmaceutically active compound. Desai's particles are a "shell of crosslinked polymer" formed by high shear conditions that create "superoxide ions that are capable of crosslinking the polymer" (col. 8 lines 35-47). In Desai, after high shear force treatment the polymer contains "small nanodroplets of the nonaqueous solvent (containing the dissolved pharmacologically active agent)." (col. 9 lines 31-35).

Furthermore, Desai does not teach sonication or any other method to cause precipitation of a pharmaceutically active compound to create particles. Instead, Desai teaches that the polymer (protein) coating may contain a liquid or solid pharmaceutically active agent. (col. 7

lines 59-60). Desai removes solvents by evaporation under reduced pressure (col. 9 lines 40-42), but does not teach that this removal of solvent precipitates the pharmacologically active agent. Also, in Example 2 (relied on by the Office) Desai teaches that the sonicator is used but the later step of evaporation at 30 mm Hg is taught as removing the methylene chloride, after which Example 2 refers to "the resulting paclitaxel particles."

Applicants have amended claims 1 and 25 to clarify that in the applicants' method sonication causes the evaporation of essentially all of the water immiscible organic solvent to cause the pharmaceutically active agent to precipitate from the organic solvent into the aqueous solution. This amendment is supported by paragraph [0037] of the specification.

Consequently, Desai does not teach one of ordinary skill in the art a method to sonicate an emulsion to remove the nonaqueous organic solvent from an emulsion to form particles by causing the pharmaceutically active agent that is dissolved in the organic solvent to precipitate into the aqueous phase. Because claims 2-7, 11, 21-24 and 30-34 are dependent on claim 1, and claims 26-29 and 35-38 are dependant upon claim 25, Desai et al. do not teach one of ordinary skill in the art the inventions claimed by claims 1-7, 11, 21-38. Reconsideration and withdrawal of the § 102(b) rejection of claims 1-7, 11 and 21-38 are respectfully believed to be appropriate for these reasons.

Concerning the first §103(a) rejection, the Office suggests that Parikh et al. discloses an organic phase namely, of mannitol, in their Example 1. However, applicants claim a water immiscible organic solvent. Mannitol is not water immiscible. Mannitol is a carbohydrate and very soluble in aqueous solutions, with a solubility of 1gram/5.5 ml of water. (See material safety data sheet from Mallinckrodt Baker, Inc. http://www.jtbaker.com/msds/englishhtml/m0806.htm, print out copy attached.)

Furthermore, Parikh does not use mannitol as an organic solvent, but instead uses mannitol to adjust the osmolarity with a concentration of 55 mg/20 mls mannitol in water. (col. 4 lines 12-13 and col. 4 lines 36-43). Putting aside this functional difference between the teaching of Parikh and the claimed invention, this disclosed mannitol concentration clearly is very much below the solubility of mannitol. More specifically, even at a concentration 66 times higher than that that used by Parikh et al., mannitol still is soluble in water. Clearly the mannitol used in Parikh et al. does not establish a separate water immiscible organic phase.

In addition, in Parikh's Example 1 cited by the Office, the pharmaceutically active compound cyclosporine does not appear to be dissolved, but instead is in suspension. (col. 4 lines 31-65). Therefore, Parikh, unlike the applicants, does not teach an emulsion composed of two phases, an aqueous phase and water immiscible organic phase with a pharmaceutically active compound dissolved in organic phase.

Because Parikh does not teach an emulsion, as applicants claim the addition of the evaporation by sonication taught by Chagnon et al. would not teach one of ordinary skill in the art applicants' claimed method of sonicating an emulsion to evaporate the water immiscible organic solvent to cause the precipitation of the pharmaceutically active substance dissolved in the organic solvent.

The Office further suggests that Parikh et al also teaches a method of precipitation; however, Parikh merely lists precipitation as a method of creating particles or reducing particle size. (col. 4 lines 6-12). Parikh, unlike applicants, does not teach any methods of precipitation, and therefore Parikh et al. does not teach that precipitation from an emulsion forms particles of pharmaceutically active substance.

Reconsideration and withdrawal of the § 103(a) rejection of claims 1 and 25 from Parikh et al. in view of Chagnon et al. are respectfully believed to be appropriate for these reasons. Applicants' claims 2-19, 21-24 and 26-38 are dependant upon either claim 1 or claim 25 and reconsideration and withdrawal of the § 103(a) rejection of these claims also are respectfully believed to be appropriate and requested.

Concerning the second §103(a) rejection, the Office suggests that Desai, uses high shear, including sonication, to prepare particles from an oil-in-water emulsion and removes solvents by evaporation. The Office also suggests that the use of sonication to remove solvent would be obvious to one of ordinary skill in the art and therefore Desai anticipates applicants' claims. However as discussed above, Desai does not teach precipitation from an emulsion to prepare particles of pharmaceutically active agent.

The Office also suggests that a portion of the organic solvent would have been removed by the method taught by Desai. While it is possible (but not explicitly taught) that high shear treatment according to the technique of Desai may remove a portion of the solvent, Desai specifies that following such high shear treatment, which can include sonication, the pharmaceutically active compound would be found dissolved in nanodroplets of nonaqueous solvent. (Col. 9, lines 29-35). Therefore unlike the applicants' amended claims 1 and 25, Desai sonication does not result in removing essentially all the organic solvent, or cause precipitation of pharmaceutically active agent. Desai as discussed above does not even specify that particle preparation involves precipitation of the pharmaceutically active agent. This lack of a precipitation step is consistent with the Desai teaching that the particle can contain the pharmaceutically active agent as either a solid or a liquid. (Col 7 lines 58-59).

The Office's suggestion, that it would have been obvious to one of ordinary skill in the art to sonicate to remove solvent, is inconsistent with Desai's requirement that solvents are evaporated under reduced pressure following a high shear treatment such as sonication. Sonication does not reduce pressure, and is not one of the "acceptable methods of evaporation including rotary evaporators, falling film evaporators, spray driers, freeze driers and the like." (Col 9 lines 40-45). Therefore, applicants' claimed invention would not have been obvious to one of ordinary skill in the art.

Reconsideration of the withdrawal of the § 103(a) rejection of claims 1 and 25 in light of Desai are respectfully believed to be appropriate for these reasons. Applicants claims 2-7 11, 21-39 are dependant upon either claim 1 or claim 25 and their allowance is respectfully believed to be in order.

Applicants have made an earnest endeavor to place this application in condition for allowance, and favorable consideration is respectfully requested. Applicants respectfully believe that these amendments place the application into condition for allowance or into better form for appeal and that entry under Rule 116 is accordingly in order. In addition, applicants respond to a matter raised for the first time in the Office Action, namely the question raised on page 8 concerning "a portion" of the solvent.

Respectfully submitted,

COOK, ALEX, MCFARRON, MANZO,
CUMMINGS & MEHLER, LTD.

Dated: January 31, 2006

By _____
Raymond M. Mehler, Reg. No. 26,306

200 West Adams Street
Suite 2850
Chicago, Illinois 60606
(312) 236-8500

MSDS Number: **M0806** * * * * * *Effective Date:* ***12/19/05*** * * * * * *Supercedes:* ***05/14/03***

MSDS Material Safety Data Sheet

From: **Mallinckrodt Baker, Inc.**
222 Rod School Lane
Phillipsburg, NJ 08865

Mallinckrodt CHEMICALS J.T.Baker

24 Hour Emergency Telephone: 908-859-2151
CHEMTREC: 1-800-424-9300

National Response in Canada
CANUTEC: 613-996-6666

Outside U.S. and Canada
Chemtrec: 703-527-3887

NOTE: CHEMTREC, CANUTEC and National Response Center emergency numbers to be used only in the event of chemical emergencies involving a spill, leak, fire, exposure or accident involving chemicals.

All non-emergency questions should be directed to Customer Service (1-800-582-2537) for assistance.

MANNITOL

1. Product Identification

Synonyms: Manna Sugar; Mannite; Mannitol,d- ; 1,2,3,4,5,6-Hexanehexol
CAS No.: 69-65-8
Molecular Weight: 182.17
Chemical Formula: C6H14O6
Product Codes:
J.T. Baker: 2553, 2554, 2555
Mallinckrodt: 6208, 6209, 6212, 7781

2. Composition/Information on Ingredients

Ingredient	CAS No	Percent	Hazardous
D-Mannitol	69-65-8	90 - 100%	Yes

3. Hazards Identification

Emergency Overview

WARNING! MAY FORM COMBUSTIBLE DUST CONCENTRATIONS IN AIR.

SAF-T-DATA(tm) Ratings (Provided here for your convenience)

Health Rating: 0 - None
Flammability Rating: 2 - Moderate
Reactivity Rating: 0 - None
Contact Rating: 1 - Slight
Lab Protective Equip: GOGGLES; LAB COAT
Storage Color Code: Green (General Storage)

Potential Health Effects

Inhalation:
Large quantities of inhaled material could cause irritation of the upper respiratory tract. A tickling cough is a common symptom.
Ingestion:
May cause gastric irritation, nausea and diarrhea. Large doses produce vomiting, chills, dizziness, chest pain, heart failure and pulmonary edema.
Skin Contact:
May cause irritation and discoloration of sensitive skin areas.
Eye Contact:
May cause irritation, redness and pain.
Chronic Exposure:
No information found.
Aggravation of Pre-existing Conditions:
No information found.

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4. First Aid Measures

Inhalation:
Remove to fresh air. Get medical attention for any breathing difficulty.
Ingestion:
If large amounts were swallowed, give water to drink and get medical advice.
Skin Contact:
Wash exposed area with soap and water. Get medical advice if irritation develops.
Eye Contact:
Wash thoroughly with running water. Get medical advice if irritation develops.

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5. Fire Fighting Measures

Fire:
As with most organic solids, fire is possible at elevated temperatures or by contact with an ignition source. Mannitol: Flash Point: > 149C (300F)

Minimum dust cloud ignition temperature: 460C (860F)
Explosion:
Fine dust dispersed in air in sufficient concentrations, and in the presence of an ignition source is a potential dust explosion hazard. Mannitol: Minimum explosible concentration = 0.065 g/l Maximum explosion pressure: 97 lb/sq. in.
Fire Extinguishing Media:
Water spray, carbon dioxide, or dry powder.
Special Information:
In the event of a fire, wear full protective clothing and NIOSH-approved self-contained breathing apparatus with full facepiece operated in the pressure demand or other positive pressure mode. Pressure from the extinguishing media may cause severe dusting.

6. Accidental Release Measures

Remove all sources of ignition. Ventilate area of leak or spill. Wear appropriate personal protective equipment as specified in Section 8. Spills: Clean up spills in a manner that does not disperse dust into the air. Use non-sparking tools and equipment. Reduce airborne dust and prevent scattering by moistening with water. Pick up spill for recovery or disposal and place in a closed container.

7. Handling and Storage

Keep in a tightly closed container, stored in a cool, dry, ventilated area. Protect against physical damage. Isolate from any source of heat or ignition. Containers of this material may be hazardous when empty since they retain product residues (dust, solids); observe all warnings and precautions listed for the product.

8. Exposure Controls/Personal Protection

Airborne Exposure Limits:
None established.
Ventilation System:
In general, dilution ventilation is a satisfactory health hazard control for this substance. However, if conditions of use create discomfort to the worker, a local exhaust system should be considered.
Personal Respirators (NIOSH Approved):
For conditions of use where exposure to dust or mist is apparent and engineering controls are not feasible, a particulate respirator (NIOSH type N95 or better filters) may be worn. If oil particles (e.g. lubricants, cutting fluids, glycerine, etc.) are present, use a NIOSH type R or P filter. For emergencies or instances where the exposure levels are not known, use a full-face positive-pressure, air-supplied respirator. WARNING: Air-purifying respirators do not protect workers in oxygen-deficient atmospheres.

Skin Protection:
Wear protective gloves and clean body-covering clothing.
Eye Protection:
Use chemical safety goggles. Maintain eye wash fountain and quick-drench facilities in work area.

9. Physical and Chemical Properties

Appearance:
White powder.
Odor:
Odorless.
Solubility:
1 gram/5.5 ml of water.
Relative Density:
1.52
pH:
No information found.
% Volatiles by volume @ 21C (70F):
0
Boiling Point:
290 - 295C (554 - 563F)
Melting Point:
ca. 167C (ca. 333F)
Vapor Density (Air=1):
No information found.
Vapor Pressure (mm Hg):
No information found.
Evaporation Rate (BuAc=1):
No information found.

10. Stability and Reactivity

Stability:
Stable under ordinary conditions of use and storage.
Hazardous Decomposition Products:
Carbon dioxide and carbon monoxide may form when heated to decomposition.
Hazardous Polymerization:
Will not occur.
Incompatibilities:
Strong oxidizers.
Conditions to Avoid:
Heat, flames, ignition sources and incompatibles.

11. Toxicological Information

Mannitol: Oral rat LD50: 13,500 mg/kg. Investigated as a tumorigen and mutagen.

--------\Cancer Lists\----------

Ingredient	---NTP Carcinogen--- Known	Anticipated	IARC Category
D-Mannitol (69-65-8)	No	No	None

12. Ecological Information

Environmental Fate:
No information found.
Environmental Toxicity:
No information found.

13. Disposal Considerations

Whatever cannot be saved for recovery or recycling should be managed in an appropriate and approved waste disposal facility. Processing, use or contamination of this product may change the waste management options. State and local disposal regulations may differ from federal disposal regulations. Dispose of container and unused contents in accordance with federal, state and local requirements.

14. Transport Information

Not regulated.

15. Regulatory Information

--------\Chemical Inventory Status - Part 1\----------

Ingredient	TSCA	EC	Japan	Australia
D-Mannitol (69-65-8)	Yes	Yes	Yes	Yes

--------\Chemical Inventory Status - Part 2\----------

Ingredient	Korea	--Canada-- DSL	NDSL	Phil.
D-Mannitol (69-65-8)	Yes	Yes	No	Yes

--------\Federal, State & International Regulations - Part 1\----------

Ingredient	-SARA 302- RQ	TPQ	------SARA 313------ List	Chemical Catg.
D-Mannitol (69-65-8)	No	No	No	No

--------\Federal, State & International Regulations - Part 2\----------

Ingredient	CERCLA	-RCRA- 261.33	-TSCA- 8(d)
D-Mannitol (69-65-8)	No	No	No

Chemical Weapons Convention: No TSCA 12(b): No CDTA: No
SARA 311/312: Acute: No Chronic: No Fire: Yes Pressure: No
Reactivity: No (Pure / Solid)

Australian Hazchem Code: None allocated.
Poison Schedule: None allocated.
WHMIS:
This MSDS has been prepared according to the hazard criteria of the Controlled Products Regulations (CPR) and the MSDS contains all of the information required by the CPR.

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16. Other Information

NFPA Ratings: Health: **1** Flammability: **1** Reactivity: **0**
Label Hazard Warning:
WARNING! MAY FORM COMBUSTIBLE DUST CONCENTRATIONS IN AIR.
Label Precautions:
Store in a tightly closed container.
Avoid dust cloud in presence of an ignition source.
Maintain adequate ventilation.
Label First Aid:
Not applicable.
Product Use:
Laboratory Reagent.
Revision Information:
MSDS Section(s) changed since last revision of document include: 3.
Disclaimer:
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